## REMARKS

Claims 1 and 3-43 are pending. Of those claims, claims 3, 5, 9, 12-18, 21-22 and 25-43 are withdrawn. Claims 1, 5, 9, 12-14, 16 and 18 have been amended.

Applicants have amended claim 1 to specify that the tumor cells of the cytokine-expressing cellular vaccine are selected from the group consisting of allogeneic and bystander cells. Support for this amendment is provided, for example, at specification page 4, lines 3-4; and page 12, lines 18-21.

Applicants have amended claims 5, 9, 12-14, 16 and 18 to recite proper claim dependencies.

None of the amendments introduces new matter.

## THE OBJECTIONS

### *The Claims*

The Examiner has objected to claims 1, 4, 6-8, 10, 19-20, 23 and 24 because they read on non-elected embodiments of the invention and has requested appropriate correction.

Applicants respectfully submit that no correction is necessary at this time. Applicants note that they elected the species anti-OX40 antibody for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Applicants submit that claims 1, 4, 6-8, 10, 19-20, 23 and 24 are generic and encompass the elected species, anti-OX40 antibody. Accordingly, applicants request that the Examiner withdraw this objection.

## THE REJECTIONS

**35 U.S.C. § 112, first paragraph (enablement)**
*Claims 1, 4, 6-8, 10, 11, 19, 20, 23 and 24*

The Examiner has maintained the rejection of claims 1, 4, 6-8, 10, 11, 19, 20, 23 and 24 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner contends that the specification does not provide a sufficient enabling description of a method for cancer therapy comprising administering a cellular vaccine. Specifically, the Examiner states that the disclosed examples presented in applicants' previous arguments appear to be prophetic rather than working examples. The Examiner concludes that given the unpredictability of the art of cancer therapy, the skilled worker would require extensive and undue experimentation to practice the claimed invention. Applicants traverse.

Contrary to the Examiner's contentions, the specification discloses working examples that provides adequate enablement for the claimed invention. The specification discloses that results from animal model experiments have convincingly demonstrated that proliferation-incompetent tumor cells engineered to secrete GM-CSF are able to induce an immune response against parental, non-transduced tumor cells (*see, e.g.*, p. 29, lines 8-10). The specification discloses that vaccination of proliferation-incompetent tumor cells engineered to secrete GM-CSF stimulates potent, long-lasting and specific anti-tumor immunity that prevents tumor growth in a majority of mice challenged with non-transduced tumor cells (*see, e.g.*, p. 5, line 10 to p. 6, line 2; p. 29, line 2 to p. 30, line 4; p. 31, lines 21-23; p. 39, line 28 to p. 40, line 11; p. 40, line 23 to p. 41, line 2; and Figures 1A and 1B). The specification discloses administration into

patients of allogeneic and autologous cancer cells engineered to secrete GM-CSF for the treatment of cancer (*see*, *e.g.*, p. 29, line 12 to p. 30, line 4).

The specification also discloses that the combination of the cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF and at least one additional cancer therapeutic agent increases the efficacy of anti-tumor protection. For example, the specification discloses that, in contrast to the ineffectiveness of anti-CTLA-4 antibody monotherapy, treatment with the combination of proliferation-incompetent tumor cells that express GM-CSF and anti-CTLA-4 antibody prevented tumor growth in a majority of mice challenged with non-transduced tumor cells (*see*, *e.g.*, p. 63, line 29 to p. 64, line 20; and Figures 2A-2B). The specification also discloses that administration of the combination of proliferation-incompetent tumor cells that express GM-CSF and anti-4-1BB antibody enhanced both the number of tumor free mice and survival relative to the administration of proliferation-incompetent tumor cells that express GM-CSF alone (*see*, *e.g.*, p. 66, line 18 to p. 67, line 11; and Figures 4A-4B). The specification discloses further examples of additional combinations that demonstrate enhanced anti-tumor protection and efficacy including combinations with interferon-alpha (*see*, *e.g.*, p. 68, line 18 to p. 69, line 2; and Figures 7A-7B), docetaxel (*see*, *e.g.*, p. 69, line 13 to p. 70, line 17; and Figures 8A-8D), COX-2 inhibitor (*see*, *e.g.*, p. 70, lines 21-27; and Figures 9A-9B), CD40 ligand (*see*, *e.g.*, p. 71, line 29 to p. 72, line 3; and Figure 11A), and anti-CD40 antibody (*see*, *e.g.*, p. 72, line 21 to p. 73, line 3; and Figures 11B-11C).

The specification also discloses that the combination of proliferation-incompetent tumor cells that express GM-CSF with OX40 ligand or anti-OX40 antibody will also increase the efficacy of anti-tumor protection (*see*, *e.g.*, p. 73, line 8 to p. 74, line 9). The specification describes that published literature and various experimental results

have demonstrated a role for the engagement of OX40 (receptor) in enhancing antitumor immunity and cites to the Weinberg *et al.* publication (J. Immunol., 164:2160-2169 (2000)) (*see*, p. 74, lines 4-6). Applicants respectfully submit that the Weinberg *et al.* publication was cited in an Information Disclosure Statement on September 2, 2004. According to the Weinberg *et al.* publication, injection of OX40 ligand or anti-OX40 antibody in vivo during tumor priming resulted in a significant improvement in the percentage of tumor-free survivors in four different murine tumors derived from four separate tissues. Based on these results and the ample disclosure provided in the specification discussed above, one of skill in the art would recognize that administering the combination of proliferation-incompetent tumor cells that express GM-CSF with anti-OX40 antibody would result in enhanced therapeutic potency and/or efficacy relative to monotherapy.

In view of the above remarks, applicants respectfully submit that the present application provides more than adequate enablement for one skilled in the art to make and use the invention without undue experimentation. Accordingly, applicants request that the Examiner withdraw the rejection.

**35 U.S.C. §§ 102(a) and (e)**
*Claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24*

The Examiner has maintained the rejection of claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24 under 35 U.S.C. §§ 102(a) and 102(e) over US Patent Publication 2003/0035790 ("Chen"). The Examiner states that Chen discloses that in a cancer vaccine approach, cancer cells are isolated from patients, transduced with the relevant genes in vitro, made proliferation-incompetent by irradiation, and administered back to the patient to enhance the patient's immune response against the tumor. The Examiner

also states that Chen discloses administering anti-OX40 antibodies together with the compositions of their invention. Applicants traverse in view of the claim amendments.

Applicants have amended claim 1 (and claims dependent therefrom) to specify that the tumor cells of said cytokine-expressing cellular vaccine are selected from the group consisting of allogeneic and bystander cells. Chen does not teach or suggest this element of the claimed invention.

Chen discloses that one approach to the treatment of metastatic carcinoma is ex vivo gene therapy or "cancer vaccine" approach (*see* paragraph [0005]). Chen discloses that in the cancer vaccine approach, cancer cells are isolated from patients, transduced with various gene vectors, expanded in vitro, and after irradiation, transplanted autologously to enhance the patient's immune response against the tumor (*see* paragraph [0005]). Thus, the cancer cells disclosed by Chen are autologous cells because they are isolated and reimplanted back into the same patient.

In contrast, the amended claims of the invention are directed to the administration of the combination of a cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF and at least one additional cancer therapeutic agent to a subject, wherein said tumor cells of said cytokine-expressing cellular vaccine are selected from the group consisting of allogeneic and bystander cells. Chen does not teach or suggest this limitation of the amended claims.

Furthermore, the claimed invention also requires that the combination of the cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF and at least one additional cancer therapeutic agent results in an enhanced therapeutic effect compared to monotherapy. Chen also does not teach or suggest this particular feature of the claimed invention. Therefore, Chen fails to teach or

suggest each and every limitation of the amended claims. Accordingly, applicants request that the Examiner withdraw this rejection.

***35 USC §101 - Nonstatutory Double Patenting***
*Claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24*

The Examiner has maintained the provisional rejection of claims 1, 4, 6-8, 10, 11, 19-20, 23 and 24 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-33 of copending Application No. 10/404,662.

Applicants request that the present basis for the provisional rejection be held in abeyance until applicants are notified that claims in the instant application are otherwise allowable.

## CONCLUSION

In view of the above, applicants request that the Examiner examine the pending claims in this application. Applicants request favorable consideration and early allowance of the pending claims.

Respectfully submitted,

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